Patent Pooling for Promoting Access to Antiretroviral Drugs (ARVs) – A Strategic Option for India

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Abstract: The current HIV/AIDS scenario in India is quite grim with an estimated 2.4 million people living with HIV/AIDS (PLHA) in 2008, just behind South Africa and Nigeria. The anti-retroviral drugs (ARVs) remain the main stay of global HIV/AIDS treatment. Over 30 ARVs (single and FDCs) available under six categories viz., NRTIs (nucleoside reverse transcriptase inhibitors), NNRTIs (non-nucleoside reverse transcriptase inhibitors), Protease inhibitors, the new Fusion inhibitors, Entry inhibitors-CCR5 co-receptor antagonists and HIV integrase strand transfer inhibitors. The major originator companies for these ARVs are: Abbott, Boehringer Ingelheim (BI), Bristol-Myers Squibb (BMS), Gilead, GlaxoSmithKline (GSK), Merck, Pfizer, Roche, and Tibotec. Beginning with zidovidine in 1987, all the drugs are available in the developed countries. In India, about 30 ARVs are available as generics manufactured by Aurobindo, Hyderabad, Andhra Pradesh; Cipla Limited, Goa; Emcure Pharmaceuticals, Pune, Maharashtra; Hetero Drugs, Hyderabad, Andhra Pradesh; Macleods Pharmaceuticals, Daman; Matrix Laboratories, Nashik, Maharashtra; Ranbaxy, Sirmour, Himachal Pradesh; and Strides Arcolab, Bangalore, Karnataka. The National AIDS Control Organization (NACO) set up in 1992 by the Govt. of India provides free ARVs to HIV positive patients in India since 2004. The drugs available in India include both single drugs and FDCs covering both first line and second line ARVs. Even while there are claims of stabilization of the disease load, there is still huge gap of those who require ARVs as only about 150,000 PLHA receive the ARVs from the Govt. and other sources. Access to ARVs therefore is still a cause of serious concern ever since India became fully Trade Related Aspects of Intellectual Property Rights (TRIPS)-complaint in 2005. Therefore, the Indian pharmaceutical companies cannot make generics for those for drugs introduced post-2005 due to product patent regime. Other concerns include heat stable, other better formulations and second line ARVs for adults and more drugs and formulations for paediatric groups, that are still to be widely available in India and other developing countries. To examine whether strong intellectual property (IP) protection systems are to be considered important barriers for the limited or lack of access to ARVs, we studied the patent profile of the ARVs of the originator companies within and outside India. We could record 93 patents in the United States Patent & Trademark Office (USPTO). The originator companies have been also aggressively filing and enforcing patents in India. There have been a few efforts by companies like Gilead and GSK to grant licenses to generic manufacturers in developing countries, ostensibly to promote access to ARVs through lower (two-tier) pricing. These steps are considered as too little and too late. There is an urgent need to look for alternative strategies to promote access to ARVs both linked to and independent of IPRs. Patent pooling as a viable strategy mooted by the UNITAID should be seriously explored to promote access to ARVs. India is ideally suited for trying out the patent pool strategy as most of the global requirement of affordable ARV drugs for HIV/AIDS treatment is sourced from Indian generic companies.

INTRODUCTION

India is one of the largest and most populated countries in the world, with over a billion inhabitants. There are currently an estimated 2.4 million Indians living with HIV/AIDS [1]. Although HIV infection emerged as late as 1986 in India, later than it did in many other countries, the infection rates rose sharply throughout the 1990s. In 1987 the Government of India launched a National AIDS Control Programme (NACP) to co-ordinate national responses which covered surveillance, blood screening, and health education [2]. By the end of 1987, of the 52,907 people tested, 135 people were found to be HIV positive and 14 had AIDS. Most of these initial cases had occurred through heterosexual sex. But at the end of the 1980s a rapid spread of HIV was observed among injecting drug users in Manipur, Mizoram and Nagaland - three north-eastern states of India bordering Myanmar (Burma). At the beginning of the 1990s, as infection rates continued to rise, responses were proportionately strengthened. In 1992, the Government of India set up the National AIDS Control Organisation (NACO), to oversee the formulation of policies, prevention work and control programmes relating to HIV and AIDS [2]. In the same year, the Government of India launched a Strategic Plan for HIV prevention. This plan established the administrative and technical basis for programme management and also set up State AIDS bodies in 25 states and 7 union territories [3]. It was able to make a number of important improvements in HIV prevention such as improving blood safety *etc.* [3].

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It is now clear that although individual states and cities in India had separate epidemics, HIV had spread to the general population by the 1990s. Currently, the epidemic affects all sectors of Indian society, even those initially considered not at risk [4].

TREATMENT FOR PEOPLE LIVING WITH HIV

Antiretroviral drugs (ARVs), which can significantly delay the progression from HIV to AIDS – have been available in developed countries since 1996 [5]. There are currently over 30 ARVs available globally [6]. These include largely NRTIs, NNRTIs, Protease inhibitors, the new Fusion inhibitors, Entry inhibitors-CCR5 co-receptor antagonists and HIV integrase strand transfer inhibitors – both single drugs and fixed dose combinations (FDCs) (Table **1**). The major originator companies include: Abbott, Boehringer Ingelheim (BI), Bristol-Myers Squibb (BMS), Gilead, GlaxoSmithKline (GSK), Merck, Pfizer, Roche, and Tibotec

Table 1. Total Antiretroviral Drugs Available

S. No.	Class	Drug		Company	Year of Approval	Remarks
		Brand Name	Active Ingredient			
1	NRTI	Retrovir	Zidovudine (AZT)	GSK	1987	
2	NRTI	Epivir	Lamivudine (3TC)	GSK	1995	
3	NRTI	Zerit	Stavudine (d4T)	BMS	1994	
4	NRTI	Videx	Didanosine (ddl)	BMS	1989	
5	NRTI	Videx EC	enteric coated didanosine (ddI EC)	BMS	2000	
6	NRTI	Ziagen	Abacavir (ABC)	GSK	1988	
7	NRTI	Viread	Tenovofir Disoproxil Fumarate (TDF)	Gilead	2002	
8	NRTI	Emtriva	Emtricitabine (FTC)	Gilead	2003	
9	NRTI	Trizivir	abacavir, zidovudine, and lamivudine (ABC, AZT and 3TC)	GSK	2000	3NRTI
10	NRTI	Combivir	lamivudine and zidovudine (3TC and AZT)	GSK	1997	2 NRTI
11	NRTI	Epzicom	abacavir and lamivudine (ABC and 3TC)	GSK	2004	2 NRTI
12	NRTI	Truvada	tenofovir disoproxil fumarate and emtricitabine (TDF and FTC)	Gilead	2004	2 NRTI
13	NNRTI	Viramune	Nevirapine (NVP)	BI	1996	
14	NNRTI	Sustiva	Efavirenz (EFV)	BMS	1998	
15	NNRTI	Rescriptor	Delavirdine (DLV)	Agouron	2003	
16	NNRTI	Intelence	Etravirine	Tibotec	2008	
17	NNRTI+NRTI	Atripla	efavirenz, emtricitabine and tenofovir disoproxil fumarate (EFV, FTC and TDF)	Gilead	2006	NNRTI+NRTI combination
18	PI	Crixivan	Indinavir (IDV)	Merck	1996	
19	PI	Viracept	Nelfinavir (NFV)	Agouron	1997	
20	PI	Invirase	Saquinavir (SQV)	Roche	1997	Withdrawn 2005
21	PI	Norvir	Ritonavir (RTV)	Abbott	2000	
22	PI	Agenerase	Amprenavir (APV)	GSK	1997	Withdrawn 2007
23	PI	-	Lopinavir (LPV)	-	2000	
24	PI	Kaletra	Lopinavir (LPV)+Ritonavir (RTV)	Abbott	2005	2 PI
25	PI	Reyataz	Atazanavir (ATV)	BMS	2003	
26	PI	Lexiva	Foseamprenavir	GSK	2003	
27	PI	Prezista	Darunvir ethanolate	Tibotec	2006	
28	PI	Aptivus	Tipranavir (TPV)	BI	2005	
29	Fusion Inhibitor	Fuzeon	Enfuvirtide (T-20)	Roche	2003	
30	Entry Inhibitors-CCR5 co-receptor antagonist	Selzentry	Maraviroc	Pfizer	2007	
31	HIV integrase strand transfer inhibitors	Isentress	Raltegravir Potassium	Merck	2007	

Source:
1. HIV prevelance data\USFDA Approved HIV AIDS Drug updated 14/05/2009
2. Electronic Orange Book updated Feb, 2009

[7]. The availability of ARV drugs began in 1987 with the zidovidine and the latest ones to be approved in 2007 are the Maraviroc [8] and Raltegravir [9] potassium marketed as Selzentry (Pfizer) and Isentress (Merck) respectively.

There are about 30 ARV drugs available in India (Table **2**). Data show that almost all classes of drugs are manufactured and sold by the generic manufacturers *viz.,* Aurobindo, Hyderabad, Andhra Pradesh; Cipla Limited, Verna Industrial Estate, Goa; Emcure Pharmaceuticals, Pune, Maharashtra; Hetero Drugs, Hyderabad, Andhra Pradesh; Macleods Pharmaceuticals, Kachigam, Daman; Matrix Laboratories, Nashik, Maharashtra; Ranbaxy, Sirmour, Himachal Pradesh; and Strides Arcolab, Anekal Taluk, Bangalore.

The drugs available in India thus include both single drug and FDCs covering both the first line and second line ARVs [10-12]. The Government of India launched the free antiretroviral treatment (ART) programme in 2004, starting with eight tertiary-level government hospitals in the six high-prevalence states of India [3]. All persons with HIV infection who are clinically eligible to receive ART are included in the Phase I of the programme. The subgroups of the people living with HIV/AIDS (PLHA) targeted on a priority basis include: (i) sero-positive mothers who have participated in the prevention of parent-to-child transmission (PPTCT) programme; (ii) sero-positive children below the age of 15 years; and (iii) people with AIDS who seek treatment in government hospitals [3]. The free ART programme envisages a comprehensive prevention, care and treatment programme, with i) standardized, simplified combination of ART regimens; ii) regular secure supply of good-quality ARV drugs; and iii) a robust monitoring and evaluation system eventually working towards universal access to care and treatment [3].

Linkages and referrals to other programmes as the prevention of parent-to-child transmission (PPTCT), programme are also being strengthened to enable women and children living with HIV/AIDS have greater access to treatment. The Phase I programme is also establishing linkages with other related national programmes as the Revised National Tuberculosis Control Programme (RNTCP), Reproductive and Child Health (RCH) Programme and the massive National Rural Health Mission (NRHM) [3].

ACCESS TO ARVs IN INDIA

Currently there are over 160 ART ARV centers in 31 States and Union Territories [6] with an estimated 140,000 patients are receiving ARVs free of cost at these centers [13]. Another 35,000 patients are receiving free ARVs at ART centers run by NGOs and other organizations [3]. The ART centres are being scaled up in a phased manner to provide free ARVs to 100,000 patients by the end of 2007 and 300,000 patients by 2011 in 250 centres across India under phase III of NACO [13]. ARV drugs including combination containing ingredients for adults are: i) Two drug combination tablets containing Stavudine and Lamivudine; ii) Two drugs combination tablets containing Zidovudine and Lamivudine; iii) Three drugs combination tablets containing Stavudine, Lamivudine and Nevirapine; iv) Three drug combination tablets containing Zidovudine, Lamivudine and Nevirapine; v) Efavirenz [3]. The following drugs are used for pediatric HIV management for children weighing up to 20 kg: FDCs i) Stavudine and Lamivudine; ii) Stavudine and Lamivudine; iii) Stavudine, Lamivudine and Nevarapine; iv) Stavudine, Lamivudine and Nevarapine; and v) Efavirenz [4]. But some drugs are still not available in India as single drugs, as per our analysis (Table **3**). These include four protease inhibitors (Agenerase, Aptivus, Lexiva, and Prezista), one NNRTI (Rescriptor) and one Fusion inhibitor (Fuzeon) [7, 14].

Thus, only about 150,000 people with HIV/AIDS access the ARVs from the public sector while some also get these through private health facilities, which dominate India's healthcare sector. But the vast majority of 2.4 million PLHA cannot afford to buy treatment privately. While the coverage of treatment continues to remain unacceptably low, improvements are being made to expand access to ARVs in a number of areas [15]. This is a massive challenge for the NACO, Govt. of India.

The HIV/AIDS is a chronic disease requiring lifelong treatment with different ARV combinations compounding the problem for people who also develop drug resistance and side effects over time [16]. Thus, increasing access to ARVs also means that an increasing number of people living with HIV in India are likely to develop resistance to the first line treatment necessitating switching over to the second line ARVs. Data from Africa show that over a five year period 22% people needed such a switch-over [16]. In addition, another study from South Africa found that within 3 years on ART, 21% of patients who had started a d4T-based regimen needed to be switched because of toxicity [17]. This resulted in a 2006 recommendation by the WHO to move away from d4T to less toxic combinations based on either AZT or tenofovir [18], of course with a significant price implications. In 2008, the NACO began to roll out government funded second-line anti-retroviral treatment in two centres in Mumbai and Chennai [6]. There are also plans to improve the provision of nevirapine to pregnant mothers with HIV, which can significantly reduce the risk that they will pass infection on to their child [6]. In common with other parts of the developing world, the second line ARV treatment in India is currently prohibitively more expensive than the first line treatment which is essentially based on the generics.

Despite several global initiatives to provide ARV treatment in poor and middle income countries, like the 3 by 5 and the current efforts towards Universal Access, the outreach is still poor with the targets well behind with coverage of an estimated 3 million or about 31% of the 9.7 million needing the ARVs [15, 16]. What is more, about 2.5 million new infections were added during 2007 underscoring the massive task ahead. Another matter of serious concern is the estimated 2.1 million children under 15 years needing

Table 2. Antiretroviral Drugs Available in India

S. No.	Class	Drug (Active Ingredient)	Company	Remarks
1	NRTI	Zidovudine (AZT)*	Ranbaxy (Sirmour, Himachal Pradesh), Aurobindo (Hyderabad, Andhra Pradesh), Cipla (Verna Industrial Estate, Goa), Matrix Laboratories (Nashik, Maharashtra), Hetero Drugs (Hyderabad, Andhra Pradesh)	Second Line
2	NRTI	Lamivudine (3TC) #	Ranbaxy (Sirmour, Himachal Pradesh), Cipla Limited (Verna Industrial Estate, Goa), Matrix Laboratories (Nashik, Maharashtra), Hetero Drugs (Hyderabad, Andhra Pradesh), Macleods Pharmaceuticals (Kachigam, Daman)	Second Line
3	NRTI	Stavudin (d4T)*	Aurobindo (Hyderabad, Andhra Pradesh), Matrix Laboratories (Nashik, Maharashtra), Cipla (Verna Industrial Estate, Goa), Emcure Pharmaceuticals (Pune, Maharashtra), Hetero Drugs (Hyderabad, Andhra Pradesh)	-
4	NRTI	Didanosine (ddl)*	Aurobindo (Hyderabad, Andhra Pradesh)	Second Line
5	NRTI	Abacavir sulfate (ABC) #	Aurobindo (Hyderabad, Andhra Pradesh), Matrix Laboratories (Nashik, Maharashtra)	Second Line
6	NRTI	Emtricitabine (FTC) #	Aurbindo (Hyderabad, Andhra Pradesh), Matrix Laboratories (Nashik, Maharashtra)	-
7	NRTI	Tenofovir disoproxil fumarate (TDF) #	Matrix Laboratories (Nashik, Maharashtra)	Second Line
8	NRTI	Abacavir, zidovudine, and lamivudine (ABC, AZT and 3TC) #	Aurbindo (Hyderabad, Andhra Pradesh)	3NRTI; Trizivir US brand name in Indian generic FDC manufactured; First Line
9	NRTI	Lamivudine and zidovudine (3TC and AZT) #	Aurobindo (Hyderabad, Andhra Pradesh), Pharmacare Ltd, Cipla (Verna Industrial Estate, Goa), Emcure Pharmaceuticals Limited (Pune, Maharashtra), Matrix Laboratories (Nashik, Maharashtra), Hetero Drugs (Hyderabad, Andhra Pradesh)	2 NRTI; Combivir US brand name in Indian generic FDC manufactured; First Line
10	NRTI	Abacavir and lamivudine (ABC and 3TC) #	Aurobindo (Hyderabad, Andhra Pradesh)	2 NRTI; Epzicom US brand name in Indian generic FDC manufactured
11	NRTI	Tenofovir disoproxil fumarate and emtricitabine (TDF and FTC) #	Matrix Laboratories (Nashik, Maharashtra), Aurobindo (Hyderabad, Andhra Pradesh)	2 NRTI; Truvada US brand name in Indian generic FDC manufactured; Second Line
12	2 NRTI	Lamivudine+Tenofovir Disoproxil Fumarate #	Matrix Laboratories (Nashik, Maharashtra)	-
13	2 NRTI	Abacavir Sulfate+Lamivudine #	Aurobindo (Hyderabad, Andhra Pradesh)	
14	3 NRTI	Lamivudine+Zidovudine+Abacavir Sulfate #	Aurbindo (Hyderabad, Andhra Pradesh)	First Line
15	NNRTI	Nevirapine (NVP) #	Ranbaxy (Sirmour, Himachal Pradesh), Aurobindo (Hyderabad, Andhra Pradesh), Cipla (Verna Industrial Estate, Goa), Strides Arcolabs (Anekal Taluk Bangalore), Hetero Drugs (Hyderabad, Andhra Pradesh), Matrix Laboratories (Nashik, Maharashtra)	First Line
16	NNRTI	Efavirenz (EFV) #	Aurobindo (Hyderabad, Andhra Pradesh), Cipla Limited (Verna Industrial Estate, Goa), Strides Arcolab (Anekal Taluk Bangalore), Matrix Laboratories (Nashik, Maharashtra), Emcure Pharmaceuticals (Pune, Maharashtra), Hetero Drugs (Hyderabad, Andhra Pradesh)	First Line
17	NNRTI	Etravirine #	Johnson & Johnson	204028; mail-box application no. IN/PCT/2001/00436/MUM

(Table 2) contd…..

S. No.	Class	Drug (Active Ingredient)	Company	Remarks
18	NNRTI+NRTI	Efavirenz, emtricitabine and tenofovir disoproxil fumarate (EFV, FTC and TDF)	Viraday is manufactured by Cipla	NNRTI+NRTI combination; Atripla US brand name in Indian generic FDC called viraday [2]
19	2 NRTI+NNRTI	Stavudine+Lamivudine+Efavirenz #	Strides Arcolab (Anekal Taluk Bangalore)	First Line
20	2 NRTI+NNRTI	Lamivudine+Zidovudine+Efavirenz #	Strides Arcolab (Anekal Taluk Bangalore), Aurobindo (Hyderabad, Andhra Pradesh)	First Line
21	2 NRTI+NNRTI	Lamivudine+Zidovudine+Nevirapine #	Aurobindo (Hyderabad, Andhra Pradesh), Cipla Limited (Verna Industrial Estate, Goa), Strides Arcolab (Anekal Taluk Bangalore)	First Line
22	2 NRTI+NNRTI	Lamivudine+Stavudine+Nevirapine #	Strides Arcolab (Anekal Taluk Bangalore)	First Line
23	PI	Indinavir (IDV) #	Cipla (Verna Industrial Estate, Goa), Emcure (Pune, Maharashtra), Hetero Drugs (Hyderabad, Andhra Pradesh), Ranbaxy (Sirmour, Himachal Pradesh)	Second Line
24	PI	Nelfinavir (NFV) #	Cipla (Verna Industrial Estate, Goa), Hetero Drugs (Hyderabad, Andhra Pradesh), Macleods Pharmaceuticals (Kachigam, Daman)	Second Line
25	PI	Ritonavir (RTV) #	Cipla (Verna Industrial Estate, Goa), Hetero Drugs (Hyderabad, Andhra Pradesh)	Second Line
26	PI	Lopinavir/Ritonavir #	Matrix Laboratories (Nashik, Maharashtra), Aurobindo (Hyderabad, Andhra Pradesh), Cipla (Verna Industrial Estate, Goa)	Second Line
27	PI	Atazanavir (ATV) #	Emcure Pharmaceuticals (Pune, Maharashtra)	Second Line
28	PI	Darunavir**	Emcure Pharmaceuticals (Pune, Maharashtra)	Second Line
28	Fusion Inhibitor	Nil		Nil
29	Entry Inhibitors-CCR5 co-receptor antagonist	Maraviroc		Patent granted in India;204132; mail-box Application No. 885/BOM/1999; Drug registration in process [1] Second Line
30	HIV integrase strand transfer inhibitors	Reltegravir Potassium		Patent granted in India; 212400; mail-box application no. 868/CHENP/2004

Approved Drugs; # Tentatively Approved.
** Registration pending with the Indian Drug Controller.
Explanation for classifying drugs (active ingredient) as First Line & Second Line
single drug- First Line- National AIDS Control Organization (NACO); National Program.
single drug- Second Line- Prioritizing Second-Line Antiretroviral Drugs for Adults and Adolescents: A Public Health Approach.
FDC- First Line- NACO+WHO guidelines.
FDC- Second Line- WHO guidelines.
Source:
1. www.jipmer.edu/charu/v4issue1.pdf
2. http://pharmacy.around-world.biz/drugs/Atripla.html
3. USFDA: HIV prevalence data\President's Emergency Plan for AIDS Relief updated 14/05/2009.
4. Prioritizing Second-Line Antiretroviral Drugs for Adults and Adolescents: a Public Health Approach (First & Second Line).

treatment while the coverage is about 10% only [15]. Funding for the purchase of the drugs remains a serious constraint with the gap between required and available resources of US$8.1 billion during 2007. To meet the universal targets, funding needs to be enhanced to at least four times to US$ 35 billion in 2010 and to US$41 billion in 2015 [15]. One critical factor continues to be the cost of ARVs [15].

IMPACT OF NEW PATENT REGIMES

In the light of the new TRIPS-complaint IP regime [19] in India and other developing countries and the need to find

Table 3. ART Drugs Not Available in India as Single Drug

S. No.	Brand Name	Class	Generic	Company Manufacturing	Applicant	Assignee
1	Rescriptor	NNRTI	Delavirdine (DLV)	Agouron (USA)	Pfizer (USA)	Pharmacia & Upjohn Co
2	Agenerase	PI	Amprenavir (APV)	GSK (UK)	GSK (UK)	Vertex Pharma GSK
3	Aptivus	PI	Tipranavir (TPV)	BI (Germany)	BI (Germany)	Pharmacia and Upjohn Co.
4	Lexiva	PI	Fosamprenavir Calcium (FOS-APV)	GSK (UK)	GSK (UK)	Vertex Pharmaceuticals
5	Prezista*	PI	Darunavir Ethanolate	Tibotec (USA),	Tibotec (USA)	Tibotec (USA)
6	Fuzeon	Fusion Inhibitor	Enfuvirtide (T-20)	Roche (Switzerland)	Roche (Switzerland) & Trimeris	Duke University Trimeris Inc.

Source:
1. HIV prevalence data/USFDA Approved HIV AIDS Drug Updated January 2008.
2. Electronic Orange Book.
3. United States Patent & Trade Mark Office.

*Registration pending with the Indian Drug Controller.

innovative strategies to provide ARVs, there is a need to have a serious look at whether the strong IP protection system is a barrier. We therefore looked at the patent profile of ARV drugs both in India and the USPTO filed by the originator companies. Table **4** shows data on the patent profile of FDA approved ARVs. We could track 93 patents on ARVs filed in the USPTO by the originator companies. The major patent filers were Abbot, Gilead, Abbott, GSK *etc.* with the number of patents filed varying with the drug. For example, Abbott filed as many as 20 patents on Lopinavir-Ritonavir (sold as Kaletra). For combinations as Atripla (Efavirenz and Emtricitabine and Tenofovir Disoproxil fumerate), Gilead filed as many as 15 patents. Similarly, Gilead also filed 10 patents on Truvada (Emtricitabine and Tenofovir Disoproxil fumarate). Data on break-up of the patents filed at the USPTO show that Gilead holds the maximum (25) patents followed by Abbott with 20, GSK with 17, Tibotec 5 *etc.,* (Table **5**).

Significantly, most generic antiretroviral agents currently now being used in Africa and Asia are manufactured in India as the Indian Patent Act (1970) permitted making generic copies of drugs in India [20]. With the largest global standard facilities for manufacturing outside the USA, the Indian companies were able to offer HIV drugs at a fraction of the cost of brand-name drugs. The new Indian patent Act (2005) has already created significant barriers for the development of new generics on ARVs patented in India after 2005 [21]. Developing countries had to allow inventors to file patent applications from January 1, 1995, and the decision on whether or not to grant any patent could be taken at the end of the transition period. This has potentially serious impact on global initiatives of MSF, PEPFAR, Clinton Foundation *etc* which source drugs from the Indian companies for distribution in African countries [20].

There are also apprehensions that the first-line antiretroviral drug regimens in wide use may soon be found wanting to meet the needs of HIV-infected patients [22]. There is also evidence to show that some people may be intolerant to some drugs as also reports of contraindications that need attention [18, 23]. More importantly, there could be treatment failure necessitating drugs outside the available ARV drug regimens. In addition, without strong second-line therapeutic regimens HIV patients could well stand to lose the benefits of antiretroviral therapy. Worse still, they may transmit the drug-resistant virus to others compounding the problem. "Sustaining" may well soon surpass with "scaling up" of antiretroviral therapy emerging as the major challenge [22]. Brazil is already facing this challenge, and African and Asian countries with far fewer resources will probably encounter even greater hurdles in gaining access to second-line therapies [22].

The impact of Trade Related Aspects of Intellectual Property Rights (TRIPs)-complaint legislation [19, 21] on access to ARVs to HIV-infected persons in resource-limited countries therefore cannot be overemphasized. There is a need to find solutions and find them fast. A dual approach may be required i) ensure the continued availability of high quality generics by manufacturers from India and elsewhere; and ii) encourage strong efforts towards developing new generics from patented drugs and new formulations through newer global strategies. For example, the US FDA has approved, under PEPFAR, several generic antiretroviral preparations for purchase and use outside the United States [10].

There have been a few attempts by the originator companies, under intense criticism on their pricing policies, to license the ARV drugs. Table **6** shows data on licensing of ARV drugs by the originator companies to non-US companies, mostly in South Africa, other African countries and India. GSK has licensed to maximum companies outside the US – 4 companies in the African continent. The BMS has licensed its drugs stavudine and didanosine to over 49 countries including India. Some companies like Gilead have licensed manufacture of its drugs to a large number of generic companies in India through non-exclusive licensing [24].

Table 4. Patent Profile of FDA Approved Drugs

S. No.	U.S. Patent No.	Active Ingredient	Proprietary	Applicant	Class	Year of Filing	Patent Expiration
1	5585397	Amprenavir	Agenerase	GSK	PI	24-Nov-93	17-Dec-2013
2	5646180	Amprenavir	Agenerase	GSK	PI	5-Dec-95	8-Jul-2014
3	5723490	Amprenavir	Agenerase	GSK	PI	19-Apr-95	3-Mar-2015
4	6730679	Amprenavir	Agenerase	GSK	PI	20-Mar-97	11-Nov-2017
5	6436989	Fosamprenavir Calcium	Lexiva	GSK	PI	24-Dec-97	24-Dec-2017
6	6514953	Fosamprenavir Calcium	Lexiva	GSK	PI	20-Apr-01	15-Jul-2019
7	5849911	Atazanavir Sulfate	Reyataz	BMS	PI	9-Apr-97	20-Jun-2017
8	6087383	Atazanavir Sulfate	Reyataz	BMS	PI	21-Dec-98	21-Dec-2018
9	5843946	Darunavir Ethanolate	Prezista	Tibotec	PI	24-Aug-93	1-Dec-2015
10	6248775	Darunavir Ethanolate	Prezista	Tibotec	PI	8-Apr-99	13-Aug-2014
11	6335460	Darunavir Ethanolate	Prezista	Tibotec	PI	22-Feb-00	25-Aug-2012
12	5413999	Indinavir Sulfate	Crixivan	Merck	PI	7-May-93	9-May-2012
13	6645961	Indinavir Sulfate	Crixivan	Merck	PI	4-Mar-98	4-Mar-2018
14	5541206	Lopinavir; Ritonavir	Kaletra	Abbott	PI	25-Apr-95	30-Jul-2013
15	5635523	Lopinavir; Ritonavir	Kaletra	Abbott	PI	6-Apr-95	3-Jun-2014
16	5648497	Lopinavir; Ritonavir	Kaletra	Abbott	PI	24-Mar-95	15-Jul-2014
17	5674882	Lopinavir; Ritonavir	Kaletra	Abbott	PI	29-Mar-95	7-Oct-2014
18	5846987	Lopinavir; Ritonavir	Kaletra	Abbott	PI	20-Mar-97	29-Dec-2012
19	5886036	Lopinavir; Ritonavir	Kaletra	Abbott	PI	20-Mar-97	19-Nov-2013
20	5914332	Lopinavir; Ritonavir	Kaletra	Abbott	PI	21-Nov-96	13-Dec-2015
21	5948436	Lopinavir; Ritonavir	Kaletra	Abbott	PI	13-Mar-95	13-Sep-2013
22	6037157	Lopinavir; Ritonavir	Kaletra	Abbott	PI	26-Jun-96	26-Jun-2016
23	6232333	Lopinavir; Ritonavir	Kaletra	Abbott	PI	7-Nov-97	7-Nov-2017
24	6284767	Lopinavir; Ritonavir	Kaletra	Abbott	PI	8-Dec-98	15-Feb-2016
25	6458818	Lopinavir; Ritonavir	Kaletra	Abbott	PI	2-Jul-99	7-Nov-2017
26	6521651	Lopinavir; Ritonavir	Kaletra	Abbott	PI	10-Sep-99	7-Nov-2017
27	6703403	Lopinavir; Ritonavir	Kaletra	Abbott	PI	20-Sep-01	26-Jun-2016
28	7141593	Lopinavir; Ritonavir	Kaletra	Abbott	PI	22-May-00	22-May-2020
29	7432294	Lopinavir; Ritonavir	Kaletra	Abbott	PI	12-Oct-06	22-May-2020
30	6911214	Lopinavir; Ritonavir	Kaletra	Abbott	PI	4-Sep-01	28-Nov-2021
31	5484801	Lopinavir; Ritonavir	Kaletra	Abbott	PI	12-May-95	28-Jan-2014
32	7148359	Lopinavir; Ritonavir	Kaletra	Abbott	PI	4-May-05	19-Jul-2019
33	7364752	Lopinavir; Ritonavir	Kaletra	Abbott	PI	10-Nov-00	10-Nov-2020
34	5484926	Nelfinavir Mesylate	Viracept	Agouron	PI	2-Feb-94	7-Oct-2013
35	5952343	Nelfinavir Mesylate	Viracept	Agouron	PI	7-Jun-95	7-Oct-2013
36	6162812	Nelfinavir Mesylate	Viracept	Agouron	PI	1-Apr-99	7-Oct-2013
37	5196438	Saquinavir Mesylate	Invirase	Roche	PI	19-Nov-90	19-Nov-2010
38	5852195	Tipranavir	Aptivus	BI	PI	4-Nov-96	22-Jun-2019
39	6147095	Tipranavir	Aptivus	BI	PI	29-Oct-99	29-Oct-2019
40	6169181	Tipranavir	Aptivus	BI	PI	9-Nov-98	6-May-2014

(Table 4) contd…..

S. No.	U.S. Patent No.	Active Ingredient	Proprietary	Applicant	Class	Year of Filing	Patent Expiration
41	6231887	Tipranavir	Aptivus	BI	PI	27-Jul-98	27-Jul-2018
42	5034394	Abacavir Sulfate	Ziagen	GSK	NRTIs	22-Dec-89	18-Dec-2011
43	5089500	Abacavir Sulfate	Ziagen	GSK	NRTIs	8-May-91	26-Jun-2009
44	6294540	Abacavir Sulfate	Ziagen	GSK	NRTIs	1-Dec-99	14-May-2018
45	6641843	Abacavir Sulfate	Ziagen	GSK	NRTIs	4-Aug-00	4-Feb-2020
46	5047407	Abacavir Sulfate; Lamivudine	Epzicom	GSK	NRTIs	8-Feb-89	17-Nov-2009
47	5905082	Abacavir Sulfate; Lamivudine	Epzicom	GSK	NRTIs	2-Jun-92	18-May-2016
48	6417191	Abacavir Sulfate; Lamivudine	Epzicom	GSK	NRTIs	30-Sep-97	28-Mar-2016
49	7119202	Abacavir Sulfate; Lamivudine	Epzicom	GSK	NRTIs	6-Jun-95	8-Feb-2009
50	6004968	Lamivudine	Epivir	GSK	NRTIs	20-Mar-98	20-Mar-2018
51	RE39155	Lamivudine	Epivir-Hbv	GSK	NRTIs	23-Jul-92	2-Jul-2013
52	5859021	Lamivudine; Zidovudine	Combivir	GSK	NRTIs	22-Feb-96	15-May-2012
53	5210085	Efavirenz; Emtricitabine; Tenofovir Disoproxil Fumarate	Atripla	Gilead	NRTIs	22-Feb-91	11-May-2010
54	5519021	Efavirenz; Emtricitabine; Tenofovir Disoproxil Fumarate	Atripla	Gilead	NRTIs	2-Jun-95	21-May-2013
55	5663169	Efavirenz; Emtricitabine; Tenofovir Disoproxil Fumarate	Atripla	Gilead	NRTIs	2-Jun-95	2-Sep-2014
56	5811423	Efavirenz; Emtricitabine; Tenofovir Disoproxil Fumarate	Atripla	Gilead	NRTIs	12-Mar-97	7-Aug-2012
57	5814639	Efavirenz; Emtricitabine; Tenofovir Disoproxil Fumarate	Atripla	Gilead	NRTIs	16-Feb-93	29-Sep-2015
58	5914331	Efavirenz; Emtricitabine; Tenofovir Disoproxil Fumarate	Atripla	Gilead	NRTIs	7-Jun-95	2-Jul-2017
59	5922695	Efavirenz; Emtricitabine; Tenofovir Disoproxil Fumarate	Atripla	Gilead	NRTIs	25-Jul-97	25-Jul-2017
60	5935946	Efavirenz; Emtricitabine; Tenofovir Disoproxil Fumarate	Atripla	Gilead	NRTIs	25-Jul-97	25-Jul-2017
61	5977089	Efavirenz; Emtricitabine; Tenofovir Disoproxil Fumarate	Atripla	Gilead	NRTIs	6-Nov-98	25-Jul-2017
62	6043230	Efavirenz; Emtricitabine; Tenofovir Disoproxil Fumarate	Atripla	Gilead	NRTIs	19-May-99	25-Jul-2017
63	6639071	Efavirenz; Emtricitabine; Tenofovir Disoproxil Fumarate	Atripla	Gilead	NRTIs	19-Oct-01	14-Feb-2018
64	6642245	Efavirenz; Emtricitabine; Tenofovir Disoproxil Fumarate	Atripla	Gilead	NRTIs	7-Jun-95	4-Nov-2020
65	6703396	Efavirenz; Emtricitabine; Tenofovir Disoproxil Fumarate	Atripla	Gilead	NRTIs	7-Jun-95	9-Mar-2021
66	6939964	Efavirenz; Emtricitabine; Tenofovir Disoproxil Fumarate	Atripla	Gilead	NRTIs	24-Jun-04	20-Jan-2018
67	7402588	Efavirenz; Emtricitabine; Tenofovir Disoproxil Fumarate	Atripla	Gilead	NRTIs	28-Mar-06	1-Feb-2010
68	5210085	Emtricitabine; Tenofovir Disoproxil Fumarate	Truvada	Gilead	NRTIs	22-Feb-91	11-May-10
69	5814639	Emtricitabine; Tenofovir Disoproxil Fumarate	Truvada	Gilead	NRTIs	16-Feb-93	29-Sep-15
70	5914331	Emtricitabine; Tenofovir Disoproxil Fumarate	Truvada	Gilead	NRTIs	7-Jun-95	2-Jul-17

(Table 4) contd…..

S. No.	U.S. Patent No.	Active Ingredient	Proprietary	Applicant	Class	Year of Filing	Patent Expiration
71	5922695	Emtricitabine; Tenofovir Disoproxil Fumarate	Truvada	Gilead	NRTIs	25-Jul-97	25-Jul-17
72	5935946	Emtricitabine; Tenofovir Disoproxil Fumarate	Truvada	Gilead	NRTIs	25-Jul-97	25-Jul-17
73	5977089	Emtricitabine; Tenofovir Disoproxil Fumarate	Truvada	Gilead	NRTIs	6-Nov-98	25-Jul-17
74	6043230	Emtricitabine; Tenofovir Disoproxil Fumarate	Truvada	Gilead	NRTIs	19-May-99	25-Jul-17
75	6642245	Emtricitabine; Tenofovir Disoproxil Fumarate	Truvada	Gilead	NRTIs	7-Jun-95	4-Nov-20
76	6703396	Emtricitabine; Tenofovir Disoproxil Fumarate	Truvada	Gilead	NRTIs	13-Mar-95	9-Mar-21
77	7402588	Emtricitabine; Tenofovir Disoproxil Fumarate	Truvada	Gilead	NRTIs	28-Mar-06	1-Feb-10
78	5563142	Delavirdine Mesylate	Rescriptor	Agouron	NNRTIs	22-Feb-94	8-Oct-2013
79	6177101	Delavirdine Mesylate	Rescriptor	Agouron	NNRTIs	7-Jun-99	7-Jun-2019
80	6238695	Efavirenz	Sustiva	BMS	NNRTIs	6-Apr-99	6-Apr-2019
81	6555133	Efavirenz	Sustiva	BMS	NNRTIs	2-Apr-01	6-Apr-2019
82	6878717	Etravirine	Intelence	Tibotec	NNRTIs	1-Nov-99	5-Nov-2019
83	7037917	Etravirine	Intelence	Tibotec	NNRTIs	5-Aug-03	5-Nov-2019
84	5366972	Nevirapine	Viramune	BI	NNRTIs	13-Jul-93	22-Nov-2011
85	5464933	Enfuvirtide	Fuzeon	Roche	Fusion Inhibitor	7-Jun-93	7-Jun-2013
86	6133418	Enfuvirtide	Fuzeon	Roche	Fusion Inhibitor	6-Nov-95	17-Nov-2014
87	6475491	Enfuvirtide	Fuzeon	Roche	Fusion Inhibitor	19-Dec-96	7-Jun-2015
88	6586430	Maraviroc	Selzentry	Pfizer	Entry Inhibitors-CCR5 co-receptor antagonist	1-Dec-99	1-Dec-2019
89	6667314	Maraviroc	Selzentry	Pfizer	Entry Inhibitors-CCR5 co-receptor antagonist	25-May-01	25-May-2021
90	7368460	Maraviroc	Selzentry	Pfizer	Entry Inhibitors-CCR5 co-receptor antagonist	3-Oct-03	25-Nov-2022
91	7169780	Raltegravir Potassium	Isentress	Merck	HIV integrase strand transfer inhibitors	1-May-03	9-Oct-2023
92	7217713	Raltegravir Potassium	Isentress	Merck	HIV integrase strand transfer inhibitors	24-Jul-06	21-Oct-2022
93	7435734	Raltegravir Potassium	Isentress	Merck	HIV integrase strand transfer inhibitors	19-Dec-06	21-Oct-2022

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OPTIONS TO PROMOTE ACCESS TO NEWER ARVs

A priority now is to, among others, find less toxic first-line ARV combinations and drug options when resistance is developed [23]. The primary issue continues to be strong TRIPS-complaint global patenting regimes which impact the key generics-producing countries such as India, Brazil, and Thailand. The MSF estimates that the ARV prices are unlikely to see the dramatic 99% drop seen for the currently used first-line ARVs - from >$10,000 per patient per year in 2000 to $87 today [16]. National Governments of developing countries will therefore have difficult choices before them like whether to treat more number of patients on more affordable ARV combinations, or fewer people on less toxic but more expensive combinations.

Simple switching over from the most commonly used d4T-based first-line ARV combination to a less toxic option involves about twice the cost [23]. And changing over to a TDF-based ARV regimen would mean a 4-11 fold price increase [23]. According to MSF's estimates, replacing d4T with a TDF-based regimen for all patients from 2008 to 2014

Table 5. Summary of US Patents on FDA Approved ART Drugs Company Wise

S. No.	Company	No. of Patents	Name of the Drug	Class
1	GSK	4	Agenerase	PI
2	GSK	2	Lexiva	PI
3	GSK	4	Ziagen	NRTIs
4	GSK	4	Epzicom	NRTIs
5	GSK	2	Epivir	NRTIs
6	GSK	1	Combivir	NRTIs
7	BMS	2	Reyataz	PI
8	BMS	2	Sustiva	NNRTIs
9	Tibotec	3	Prezista	PI
10	Tibotec	2	Intelence	NNRTIs
11	Merck	3	Isentress	HIV integrase strand transfer inhibitors
12	Merck	2	Crixivan	PI
13	Abbott	20	Kaletra	PI
14	Agouron	3	Viracept	PI
15	Agouron	2	Rescriptor	NNRTIs
16	Roche	1	Invirase	PI
17	Roche	3	Fuzeon	Fusion Inhibitor
18	BI	4	Aptivus	PI
19	BI	1	Viramune	NNRTIs
20	Gilead	15	Atripla	NRTIs
21	Gilead	10	Truvada	NRTIs
22	Pfizer	3	Selzentry	Entry Inhibitors-CCR5 co-receptor antagonist
Total		**93**		

Souce:
Electronic Orange Book updated Feb, 2009.

(based on today's prices) would mean a 4-11 fold price increase [16, 25]. Unless there are overall price reductions the overall increase of cost for ARVs. in some middle-income countries could be as high as 17-fold [16].

Besides the availability of generics for the first-line ARVs in countries with manufacturing capacity like India, Brazil, and Thailand, multiple producers and the resultant competition has actually brought down prices dramatically [16]. Globally, India is considered the "pharmacy of the developing world," as charities like MSF source over 80% of its ARVs from India as also other ARV providers like the Clinton Foundation, PEPFAR *etc*. [16, 20]. This was possible only because the pre-TRIPS patent regimes allowed the development of single drugs and FDCs, an innovation that not just simplified HIV/AIDS treatment but helped significant scale-ups. In the recent years, there have been aggressive patenting by originator companies in countries like India, Brazil and Thailand [26-28].

The global battle for affordable ARVs, thus is likely to get tougher in future. Developing countries with significant PLHA need to use all the means available including public health safeguards and flexibilities enshrined in the WTO TRIPS as reiterated in the Doha Declaration [29] that allows countries to overcome patent barriers by issuing compulsory licenses (CLs) to open the market to competition despite patent protection.

Other options open to sovereign countries include design or interpret national patent laws to limit the scope of patentability of new chemical entities with a public health priority and other strategies [30, 31]. Like, for example, the Indian Patents Act (2005) that allows pre-grant opposition [32]. In June 2008 such an opposition was successfully contested in India for the pediatric syrup formulation of NVP as the Indian patent office rejected the patent [26-28].

PATENT POOLS

In what is considered a path-breaking development, the UNITAID decided in principle in July 2008 to establish a patent pool for ARVs [33] that may hold the key for access to affordable newer ARVs in the future. This concept was originally mooted by the MSF, along with Essential Inventions to the UNITAID board in June 2006 to overcome the difficulties to access newer ARVs. As Ellen t'Hoen of

Table 6. Data on Drug Licensing of Originator Companies to Non-U.S. Countries

S. No.	Patent Holder	Drug	Non US Companies Licensed	India
1	GSK	lamivudine, zidovudine and lamivudine + zidovudine	Cipla Medpro - the third largest generic drug company in South Africa; Biotech Laboratories - a subsidiary of Afrika Biopharma to supply generic antiretrovirals to both the public and private sectors throughout sub-Saharan Africa; Feza Pharmaceuticals, Thembalami Pharmaceuticals and Aspen Pharmacare South Africa, and Cosmos Limited in Kenya [1 & 2]	NIL
2	Tibotec	darunavir (Prezista)	Aspen Pharmacare, South Africa [3]	Emcure Pharmaceuticals Ltd, India
3	BMS	atazanavir (Reyataz)	Aspen Pharmacare, South Africa [4]	Emcure Pharmaceuticals Ltd, India
4	BMS	stavudine and didanosine	Aurobindo Pharma, in 49 countries including South Africa [5]	Aurobindo Pharma, India
5	Gilead	tenofovir DF	Aspen Pharmacare, South Africa [6]	Emcure Pharmaceuticals Ltd., Hetero Drugs Ltd., Strides Arcolab Ltd, Alkem Laboratories Aurobindo Pharma FDC, JB Chemicals & Pharmaceuticals, Matrix, Medchem International, Ranbaxy, Shasun Chemicals & Drugs
6	Gilead	tenofovir disoproxil fumarate and emtricitabine	Aspen Pharmacare, South Africa, sold in 95 developing countries [7 & 8]	*Licensing information not available; Company manufacturing;Matrix Laboratories, Aurobindo
7	Pfizer	delavirdine	not-for-profit group the Concept Foundation and the International Dispensary Association, Thailand [9]	NIL
8	Merck	efavirenz	Aspen Pharmacare, South Africa [10]	*Licensing information not available; Company manufacturing; Aurobindo, Cipla Limited, Strides Arcolab, Matrix Laboratories, Emcure Pharmaceuticals, Hetero Drugs
9	GSK & BI	lamivudine+ stavudine+ nevirapine (Triomune)	Enaleni Pharmaceuticals, a subsidiary of Indian generic drugs manufacturer Cipla, South Africa [11]	NIL
10	BI	nevirapine	Aspen Pharmacare, South Africa [12]	*Licensing information not available; Company manufacturing; Ranbaxy, Aurobindo, Cipla, Strides Arcolabs, Hetero Drugs, Matrix Laboratories

Sources:
1. www.thebodypro.com/content/art11014.html - 20k -
2. http://www.empowermentsa.co.za/betalk.php?myid=27
3. http://www.tibotec.com/bgdisplay.jhtml?itemname=dw_leftblock1
4. www.medicalnewstoday.com/articles/38017.php - 59k
5. www.haiafrica.org/index.php?option=com_content&task=view&id=105&Itemid=1 - 31k
6. http://www.gilead.com/access_partnerships
7. http://investors.gilead.com/phoenix.zhtml?c=69964&p=irol-newsArticle&ID=700521&highlight
8. http://www.aegis.com/NEWS/BW/2005/BW050411.html
9. http://www.thebodypro.com/content/art11680.html
10. www.medicalnewstoday.com/articles/27787.php - 53k
11. http://icommons.org/article_print/a-sick-state-access-to-medicine-in-south-africa
12. http://www.essentialdrugs.org/edrug/archive/200312/msg00017.php

the UNITAIDS explains [34]: "A patent pool is a mechanism whereby patent owners put their patents in a 'pool' and allow others who need access to those patents to use them in exchange for a royalty payment. Patent pools have, in fact, been used to drive forward innovation in many different fields of technology, for example in the development of recording equipment, where you need multiple patents to be able to produce a certain product". Hoen considers that the patent pooling as a strategy will not only help the development of new fixed-dose combination drugs that combine multiple compounds into one pill, especially for the newer drugs and in developing fixed-dose combinations or paediatric formulations [34].

The advantages of patent pool appear to be huge. Like, for example, the development of pediatric formulations or the much-needed FDCs for less toxic first and second-line treatments. Patent filed by originator companies on individual compounds typically hamper the development of FDCs, a barrier that a patent pool would help break. Generic versions of new drugs also could be developed quickly through the patent pool as the generic companies need not wait for the 20-year patent expiration. If the patent pool is accessed by multiple companies, the resultant competition

should drive down the price, as seen for the current first line ARVs. What is more, these drugs could be exported to poor countries with HIV/AIDS load that have no manufacturing capability by countries like India, Brazil and Thailand. All these could be built into the licensing agreements with the originator companies that own the patents. But this can become successful only if the patent owning companies are willing to put their patents into the pool. Efforts are on at the UNITAID to work out the modalities of operating the proposed patent pool. In fact the recently concluded WHO Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property of the Inter-Governmental Working Group on Public Health and Innovation [35] had recommended exploring the feasibility of patent pools for diseases of the poor [36]. By the end of 2009, the UNITAID pool is eventually expected to run as a separate entity [37].

The need for affordable ARVs to vulnerable sections of society like children, pregnant women and people with HIV-TB in resource-poor countries cannot be overemphasized. The urgency is especially for the paediatric populations as, of the 22 ARVs approved by the US FDA for adults, as many as 8 are not approved for use in children while 9 do not have any pediatric formulations [38].

CONTRIBUTORSHIP

Kanikaram Satyanarayana conceived, designed and wrote the article.

Sadhana Srivastava shared in the draft preparation and participated in overall interpretation, revision and finalization of the paper.

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